UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF PENNSYLVANIA

SCOTT WHITELEY and HARRY BERGER, Individually and on behalf of all others similarly situated, Plaintiffs, v. ZYNERBA PHARMACEUTICALS, INC., ARMANDO ANIDO, and JAMES E. FICKENSCHER, Defendants.	Case No: 2:19-cv-04959-NIQA

PLAINTIFFS' CORRECTED MEMORANDUM OF LAW IN OPPOSITION TO DEFENDANTS' MOTION TO DISMISS (PURSUANT COURT ORDER D.I. 28)

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I. INTRODUCTION

Throughout the Class Period, Defendants touted the safety of Zynerba Pharmaceuticals, Inc.'s[1] only product in development-- a transdermal cannabinoid-based ("CBD") treatment called Zygel-- as compared to orally administered CBD alternatives. However, in reality, and unbeknownst to investors, Zygel caused devastating numbers of treatment related safety events in child and adolescent patients with developmental and epileptic encephalopathies ("DEE") during Phase II clinical testing (the "BELIEVE 1" trial). Indeed, at no time while touting Zygel's safety during the Class Period did Defendants reveal that 96% of the 46 young patients treated with Zygel during the BELIEVE 1 trial experienced a treatment emergent adverse event ("TEAE"), 60% experienced a treatment related adverse event ("TRAE"), and a staggering 25% suffered serious adverse events ("SAEs").

With no FDA approved products generating revenue, and- as Defendants admit- fully dependent on Zygel's future commercialization for Zynerba's survival, Defendants withheld this material adverse safety information until ***two months after*** the trial concluded, thus enabling the Company to raise much needed funds to continue its development activities. Defendants statements regarding Zygel's safety for child and adolescent DEE patients, all current or historical statements, are actionable. They chose to speak about Zygel's safety and thus incurred a duty to speak fully and truthfully about the adverse events that emerged during clinical testing. Moreover, Item 303 of Regulation S-K imposed a duty on Defendants to disclose the material adverse safety issues from the BELIEVE 1 trial known to Defendants, given their likely impact on Zynerba's operations.

[1] "Zynerba" or the "Company"

Moreover, the following allegations from the Complaint, assessed holistically, adequately plead that Defendants acted with the required fraudulent intent: 1) Zygel is Zynerba's only therapy in development, *i.e.*, its core (indeed, only) operation; 2) the Company had ongoing FDA-mandated SAE reporting obligations necessitating that Defendants stay apprised of all adverse safety events as they occurred; 3) Zynerba had only 25 full-time employees during the Class Period; 4) each Defendant had access to Zynerba's safety database, which contained real time (or near real time) adverse event data from the BELIEVE 1 trial during the Class Period; 5) the magnitude of the safety events in question in the BELIEVE 1 trial, which tested Zygel for the first time on adolescents and children suffering from DEE (whereas prior Phase 1 clinical testing in adults yielded positive safety results); and 3) while in possession of the adverse, material, non-public safety data, Defendants chose to cause Zynerba to sell its own shares at market prices, netting $27 million.

With actionable misstatements and scienter adequately pled, and all other elements of the claim conceded, this Court should deny Defendants' Motion[2].

II. FACTS

A. Background

Defendant Zynerba is a small clinical stage specialty pharmaceutical company with only 25 full-time employees. ¶¶ 2, 13, 20[3]. Zynerba, which has lost money since its inception, has no FDA approved products for sale and only one product in its pipeline-- Zygel. Zygel contains CBD,

[2] "Motion" refers to Defendants' Motion To Dismiss The Amended Class Action Complaint and accompanying Memorandum in Support. Dkt. No. 24-1.

[3] Citations to "__¶" are to paragraphs of the Amended Class Action Complaint ("Complaint"), Dkt. No. 21. Citations to "Defs. Br. at __" are to pages of Defendants' Memorandum in Support of their Motion to Dismiss the Amended Class Action Complaint, Dkt. No. 24-1. Citations to "Defs.' Ex. __" are to Exhibits to the Declaration of Michael S. Doluisio, attached to Defendants' Memorandum in Support of their Motion to Dismiss.

the primary non-psychoactive component of cannabis, and aims to treat four types of progressive neuropsychiatric disorders, including DEE. ¶¶ 2, 3. The drug is still at the trial stage and has not been approved for commercialization by the FDA. ¶¶ 2, 3, 19.

Zynerba has been operating at a loss since its inception. As the Company has conceded, it therefore required "[s]ubstantial additional financings … to fund its operations, to complete clinical development of and to commercially develop its product candidates." (Defs. Ex. F, at 9). Zynerba has made clear that it would not be profitable until it could successfully commercialize Zygel, its sole product, which could only occur if Zygel receives FDA approval. ¶ 20.

B. The BELIEVE 1 Trial

Clinical testing of drugs like Zygel occurs in three phases. The FDA considers all the clinical trials results and nonclinical studies in determining whether to approve a drug for market. On April 10, 2018, Defendants announced that the Company had initiated the Phase II trial for Zygel called "BELIEVE 1," a six-month open label multi-dose clinical trial, to evaluate the efficacy and safety of Zygel in children and adolescents with DEE ("April 10, 2018 Announcement"). ¶ 23. An open-label trial, as opposed to one that is blind or double-blind, is one in which both the researchers and trial patients know which treatment the patient is receiving. *Id*. Zynerba maintained a database to track any safety events that occurred during clinical testing of Zygel. *Id*.

Patients enrolled in the BELIEVE 1 trial began receiving treatment for a two-week titration period, followed by a 24-week maintenance dosing period, at the beginning of 2019. During that time, a staggering percentage of patients treated with Zygel suffered safety events. Those events were entered in Zynerba's safety database, accessible by Defendants, and Defendants reported all

"serious adverse drug experiences" to the FDA within 15 days per FDA regulations. ¶¶ 5, 22. By July 15, 2019 at the latest, the trial had concluded.

C. Misleading Statements and Omissions

To ensure its survival, Defendants had to convince investors of Zygel's prospects, with assurances of safety and efficacy, in order to raise essential financing and continue to sell its stock. Indeed, throughout the Class Period, Defendants issued misleading statements continually touting Zygel's safety, with nary a mention of the voluminous adverse safety issues that they observed during the BELIEVE 1 trial, and of which they had actual knowledge, or the risks those events posed to the continued development and commercialization of its only product. ¶¶ 19, 26-44.

For example, on Zynerba's website, Defendants advertised Zygel as "address[ing] limitations of current [CBD] treatments." ¶ 26. The Company specifically compared the safety benefits of Zygel, a transdermal CBD product, to oral administration of CBD medications, and stated that Zygel "result(s) in a lower incidence of gastrointestinal side effects …" and "transdermal delivery of Zygel avoids the gastrointestinal tract and potential degradation to THC in stomach acid, which should minimize the risk of negative psychoactive effects." ¶¶ 19, 26.

Defendants' ruse worked. In the second quarter of 2019, the Company successfully raised $27 million. ¶ 39. With no other means of generating cash to ensure its existence through the remaining and most costly phase of clinical testing, New Drug Application ("NDA") submission, and commercialization, Zynerba continued to mislead the market in order to generate financing. On August 6, 2019, Zynerba filed a registration statement on the Form S-3, which the SEC declared effective on August 13, 2019 ("August 6, 2019 Registration Statement"). Chen Decl. [4]

[4] Plaintiffs cite to the Declaration of Jing Chen in Support of Plaintiffs' Opposition to Defendants' Motion to Dismiss as "Chen Decl. Ex. __." The Court may take judicial notice of the exhibits to the Chen Decl. because they are integral to or explicitly relied upon in the Complaint. "Documents 'integral to or explicitly relied upon in the complaint' and related matters of public record may be

Ex. 1. On August 30, 2019, Zynerba filed a prospectus, with the purpose of raising an additional $75 million in financing ("August 30, 2019 Prospectus"). Chen Decl. Ex. 2; ¶ 42. Although Zynerba filed these two documents well after the completion of the BELIEVE 1 trial, Defendants omitted any mention of the adverse safety results, instead emphasizing the benefits of Zygel for young patients with DEE as compared to alternatives. ¶ 42.

D. Zynerba Belatedly Announced the Adverse Safety Results of the Trial, Causing Its Stock Price to Plunge.

On September 18, 2019, two months after the completion of the BELIEVE 1 trial, Zynerba revealed for the first time that for patients treated with Zygel, the rate of TEAEs was 96% and the rate of TRAEs was 60%. ¶ 45. Over 25% of these young trial patients suffered serious adverse events ("SAE"). *Id.* Eight patients discontinued the study due to safety events. *Id.* Shocked by the news, investors fled the stock causing the price per share to drop precipitously 22% intraday on heavy volume. ¶ 46.

III. ARGUMENT

A. Applicable Standards

When analyzing a complaint for failure to state a claim pursuant to Fed. R. Civ. P. 12(b)(6), all factual allegations are taken as true and construed in the light most favorable to the non-moving party. *See Tellabs, Inc. v. Makor Issues & Rights, Ltd.*, 551 U.S. 308, 322 (2007). To survive a motion to dismiss, the Complaint need only contain sufficient factual matter to state a claim for relief that is plausible on its face. *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009) (citing *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007)). The Third Circuit has explained that even after

considered on a motion to dismiss." *In re U.S. Interactive, Inc.*, No. 01-CV-522, 2002 WL 1971252, at *4 (E.D. Pa. Aug. 23, 2002) (*quoting In re Burlington Coat Factory Sec. Litig.*, 114 F.3d 1410, 1426 (3d Cir. 1997).

Twombly and *Iqbal,* stating a claim "'does not impose a probability requirement at the pleading stage,' but instead 'simply calls for enough facts to raise a reasonable expectation that discovery will reveal evidence of the necessary element." *Phillips v. Cty. of Allegheny*, 515 F.3d 224, 234 (3d Cir. 2008).

To state a claim for securities fraud under Rule 10b-5, a plaintiff must allege (1) the purchase of a security; (2) a material misrepresentation or omission by the defendant; (3) scienter; (4) reliance upon the misrepresentation or omission; (5) economic loss; and (6) loss causation. *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 36 (2011). Defendants only challenge falsity and scienter, thus conceding the other elements of the claim.

Claims under Rule 10b-5 are subject to the pleading standards of the Private Securities Litigation Reform Act ("PSLRA") and Fed. R. Civ. P. 9(b), requiring that allegations of fraud be stated with particularity. 15 U.S.C. § 78u-4(b). Moreover, as Defendants' own citation states, "in applying Rule 9(b), courts should be 'sensitive' to situations in which 'sophisticated defrauders' may 'successfully conceal the details of their fraud.' *In re Rockefeller Ctr. Properties, Inc. Sec. Litig.*, 311 F.3d 198, 216 (3d Cir. 2002). "Where it can be shown that the requisite factual information is peculiarly within the defendant's knowledge or control, the rigid requirements of Rule 9(b) may be relaxed." *Id.*

The Complaint sufficiently alleges that Defendants knowingly, or at minimum recklessly, failed to disclose material adverse safety events during the Class Period, including, *inter alia* that 21% of child and adolescent participants in the BELIEVE 1 trial suffered SAEs. For the following reasons, this Court should therefore deny Defendants' Motion.

B. Defendants' Class Period Statements are Actionably Misleading

Under Rule 10b-5, it is unlawful for a person "to make any untrue statement of a material fact or to omit to state a material fact necessary in order to make the statements made, in light of the circumstances under which they were made, not misleading." 17 C.F.R. § 240.10b-5. As the PSLRA requires, the Complaint identifies each misleading statement, who made the statement, and explains in detail how they misled investors. *Id.*; *Tellabs,* 551 U.S. at 321; 15 U.S.C. § 78u-4(b)(1). Specifically, while touting their clinical program for Zygel and the safety benefits of its transdermal CBD treatment as compared to orally administered CBD, Defendants knew but failed to disclose that ***almost all*** patients enrolled in the BELIEVE I trial suffered TEAEs, ***a majority*** also suffered TRAEs, and ***more than one fifth*** suffered SAEs, triggering a heightened risk to the continued development of Zygel and the Company's prospects for obtaining regulatory approval to market Zygel for the treatment of DEE in children and adolescents.

In accordance with the Exchange Act and Item 303 of Regulation S-K, Defendants had a duty to disclose this material adverse safety data because they opted to speak about Zygel's safety as compared to orally administered alternatives on Zynerba's website, and while discussing the BELIEVE 1 trial in SEC filings, generically warning of possible risks, Defendants already had access to safety data demonstrating that those risks had transpired. *See Oran v. Stafford*, 226 F.3d 275, 285–86 (3d Cir. 2000) (citations omitted) ("duty to disclose may arise when there is insider trading, a statute requiring disclosure, or an inaccurate, incomplete or misleading prior disclosure").

1. Defendants Had a Duty to Disclose the Adverse Safety Data, Including the High Rate of SAEs, From the BELIEVE 1 Trial During the Class Period

Defendants contest their duty to disclose based on the false premise that they made no statements regarding Zygel's side effects or safety related risks. Defs.' Br. at 27. Not so. Throughout the Class Period, Defendants not only issued statements discussing the BELIEVE 1

trial and the "[c]ompelling rationale for [the] utility of CBD in DEE" based on "clinical data," but also stated at all relevant times on the Company's website that Zygel "address[es] limitations of current treatments," that compared to orally administered CBD, Zygel "result(s) in a lower incidence of gastrointestinal side effects …," and "transdermal delivery of Zygel avoids the gastrointestinal tract and potential degradation to THC in stomach acid, which should minimize the risk of negative psychoactive effects." ¶ 26. They further misled the market with ineffectual and generic warnings that "Zygel may not have favorable results," when in fact the unfavorable data already existed. ¶ 31. By making these statements, Defendants undertook a duty to speak fully regarding known material adverse safety data that put the Zygel clinical program at risk and belied their claims of Zygel's safety benefits over alternatives.

Defendants' statements both before and during the Class Period touting Zygel's safety and tolerance based on Phase 1 trial results made it imperative that Defendants speak fully and truthfully *during* the Class Period regarding the material adverse safety data from the BELIEVE 1 trial. ¶ 23. Specifically, Defendants claimed that Phase I trials completed in mid-2016 on adult patients demonstrated that Zygel, "was safe and well-tolerated at all tested dose levels and the incidence of adverse events associated with [Zygel] was similar to placebo for both healthy subjects and epilepsy patients." Defs.' Ex A, at 16-17. Having previously disclosed data demonstrating Zygel's safety in Phase I testing on adult trial participants, having boasted of the lower incidence of side effects for Zygel as compared to oral CBD alternatives on Zynerba's website throughout the Class Period, and knowing (or recklessly disregarding) that the BELIEVE 1 clinical trial data showed material adverse safety issues in children and adolescents suffering from DEE treated with Zygel, Defendants had a duty to disclose the magnitude of the TEAEs, the TRAEs and, in particular, the SAEs that BELIEVE 1 trial participants suffered. *See Utesch v.*

Lannett Co., Inc., 385 F. Supp. 3d 408, 420 (E.D. Pa. 2019) (quoting *In re Vivendi, S.A. Sec. Litig.*, 838 F.3d 223, 250 (2d Cir. 2016)) ("the individual allegations cannot be viewed in isolation from one another—rather, they must be 'taken together and in context').

Defendants assert that if this Court finds a duty to disclose here, it will have the effect of establishing that all pharmaceutical companies have a "duty immediately to disclose each and every adverse event, as soon as it arises during a clinical trial." Such a requirement, Defendants argue, "would lead to absurd results and incredible burdens on pharmaceutical companies." Defs.' Br. at 28. That is not what the Complaint alleges. Instead, the Complaint alleges that Defendants have a duty to disclose material adverse safety data when they choose to speak about their product's safety-- particularly as compared to alternative available products-- and the possibility of adverse data when there is already evidence that such adverse data exists**.** *Matrixx,* 563 U.S. at 45 ("companies can control what they have to disclose ... by controlling what they say to the market.").

Defendants' reliance on *In re Adolor Corp. Sec. Litig.*, 616 F. Supp. 2d 551 (E.D. Pa. 2009) is therefore misplaced. The *Adolor* defendants had never discussed the efficacy of their trial drug. As such, the defendants there had never put the drug's efficacy in play and had no duty to disclose the drug's efficacy in any specific subgroup of patients. Here, Defendants chose to discuss Zygel's safety advantages during the Class Period. ¶ 26; Defs.' Ex. A. By putting the topic of Zygel's safety "in play," Defendants undertook an affirmative duty to disclose that although Zygel avoids certain side effects, it could create other severe side effects. *See In re Merck & Co., Sec., Derivative, & ERISA Litig.*, MDL No. 1658 (SRC), 2011 WL 3444199, at *9 (D.N.J. Aug. 8, 2011) ("[o]nce a defendant makes an affirmative statement or characterization about its business, it puts that

subject 'in play' and assumes a duty, under the securities laws, to speak truthfully about that subject") (quoting *Shapiro v. UJB Fin. Corp.,* 964 F.2d 272, 282 (3d Cir. 1992)).

Defendants' assertions that the adverse safety data was "meaningless" are similarly ineffectual. Defs.' Br. at 28. As evidenced by the 22% drop in the Company's stock price on the day of the corrective disclosure, the fact that trial participants suffered TEAEs at a rate of ***96%***, TRAEs at a rate of ***60%***, and that ***ten out of forty-eight trial*** patients reported SAEs, was far from "meaningless." *In re Innocoll Holdings Pub. Ltd. Co. Sec. Litig.*, No. CV 17-341, 2020 WL 1479128, at *14 (E.D. Pa. Mar. 25, 2020) ("Because the concept of materiality translates into information that alters the price of the firm's stock when operating in an efficient market, information disclosed is immaterial if the disclosure had no effect on stock prices.") (citation and quotations omitted). Defendants' reliance on *In re Donald J. Trump Casino Sec. Litig.-Taj Mahal Litig.*, 7 F.3d 357, 375 (3d Cir. 1993), in a backdoor attempt at disputing materiality,[5] is therefore unavailing. *Id.. See Oran*, 226 F.3d at 285 (complaint adequately pleads materiality by reference to the stock price decline on the corrective disclosure). The significance, *i.e.,* materiality, of the undisclosed safety data to investors is further apparent because Zynerba does not have any FDA approved product in its arsenal or any other therapy in its pipeline. Given Defendants' claims that Zygel's competitive advantage over alternative products relate to its safety, it is reasonable to presume that investors would have found data regarding adverse safety events from the BELIEVE 1 trial particularly significant. This is especially so given that the children and adolescents treated in the BELIEVE 1 clinical trial suffered safety events that are not symptoms of DEE. The far-

[5] "Materiality is a mixed question of law and fact. . . . Only if the alleged misrepresentations or omissions are so obviously unimportant to an investor that reasonable minds cannot differ on the question of materiality is it appropriate for the district court to rule that the allegations are inactionable as a matter of law." *Shapiro*, 964 F.2d at 280 n.11, *as amended* (May 27, 1992) (quoting *TSC Indus., Inc. v. Northway, Inc.*, 426 U.S. 438, 450 (1976)).

reaching implications of this are that a reasonable investor could also expect such safety events to occur in any child or adolescent treated with Zygel, regardless of their underlying condition.[6]

Defendants argue that the statements on Zynerba's website cannot give rise to a duty to disclose because they are true. Specifically, Defendants claim that the website accurately states that Zygel "'***may*** result in "lower incidence of gastrointestinal side effects.'" Def. Br. at 29 (emphasis added). This is as misleading as it is false. The website does not qualify the statement with the word, "may." Defendants explicitly state that Zygel's transdermal method of delivery results in a lower incidence of gastrointestinal side effects, not ***may***. Regardless, Defendants knew that children and adolescents in the BELIEVE 1 clinical trial suffered SAEs at an order of magnitude greater than adults from previous studies. Nevertheless, though opting to speak about side effects on the website, Defendants omitted the material adverse safety data from the trial.[7] Moreover, it is of no moment that this quote appears under the title, "Potential Benefit of Zygel," as Defendants argue. Defs.' Br. at 28. Defendants used the word "potential" to refer to the "potential" for lower dose levels and fewer drug interactions, not a lower incidence of side effects.

[6] Defendants offer no counter-inference, and even if they did, this Court must draw all reasonable inferences in Plaintiffs' favor. *See In re Urban Outfitters, Inc. Sec. Litig.*, 103 F. Supp. 3d 635, 645 (E.D. Pa. 2015) (quoting *Phillips*, 515 F.3d at 233) (In reviewing a motion to dismiss under Fed.R.Civ.P. 12(b)(6), [c]ourts must 'accept all factual allegations as true, construe the Complaint in the light most favorable to the plaintiff, and determine whether, under any reasonable reading of the Complaint, the plaintiff may be entitled to relief.'") (internal citation omitted).

[7] Defendants argue that the Complaint fails to allege that the adverse safety data from the BELIEVE 1 trial had anything to do with gastrointestinal side effects. Defs.' Br. at 30. This is a red herring. The exact adverse reactions the BELIEVE 1 clinical trial participants suffered is irrelevant. Once Defendants raised the subject of side effects, they had a duty to speak fully. Specifically, Defendants are not permitted to reassure investors with statements that Zygel has a lower incidence of gastrointestinal side effects without explaining that Zygel also causes an astounding number of other side effects.

Whether the website excerpt is "literally accurate" is not exculpatory.[8] "[S]tatements, although literally accurate, can become through their context and manner of presentation, devices which mislead investors. For that reason, the disclosure required by the securities laws is measured not by literal truth but by the ability of the material to accurately inform rather than mislead prospective buyers." *In re Merck,* 2011 WL 3444199, at *9 (citation omitted). A reasonable investor reads a public statement in context, not in isolation. *See Omnicare, Inc. v. Laborers Dist. Council Const. Indus. Pension Fund*, 575 U.S. 175, 190 (2015). In other words, the securities laws foreclose defendants from emphasizing favorable data while withholding material adverse information, as Defendants do here. *SEB Inv. Mgmt. AB v. Endo Int'l, PLC*, 351 F. Supp. 3d 874, 902 (E.D. Pa. 2018) (denying motion to dismiss, holding that emphasizing positive abuse data with respect to an opioid required defendants to disclose an increase in intravenous use). When internal information directly contradicts public disclosures, registrants are duty-bound to disclose it. *Cf. Hall v. Johnson & Johnson*, No.: 18-1833 (FLW), 2019 WL 7207491, at *18 (D.N.J. Dec. 27, 2019) (company cannot say talc is safe and asbestos-free when internal documents contradict it); *Endo Int'l*, 351 F. Supp. 3d at 902.[9]

[8] Defendants do not challenge the allegation that the other alleged misleading statement on their website, that "transdermal delivery of Zygel avoids the gastrointestinal tract and potential degradation to THC in stomach acid, which should minimize the risk of negative psychoactive effects," is misleading for failure to disclose the material adverse safety data, and thus concede that it is actionable.

[9] In *Endo International*, Judge Savage cited *Schueneman v. Arena Pharm., Inc.*, 840 F.3d 698, 707–08 (9th Cir. 2016), where the Ninth Circuit, reversing dismissal of a complaint, found that in the context of expressing confidence in ultimate FDA approval of a drug, the defendants touted positive results from animal studies when the animal studies actually were adverse. 351 F. Supp. 3d at 902 The Ninth Circuit found that the defendants were duty-bound to disclose the adverse animal studies and that their duty was clear, supporting that they acted with requisite fraudulent intent. *Id.* (citing *Schueneman*, 840 F.3d at 708).

In addition, Defendants' risk disclosures themselves triggered a duty to disclose the adverse safety data. "[A] company may be liable under Section 10b for misleading investors when it describes as hypothetical a risk that has already come to fruition." *Williams v. Globus Med., Inc.*, 869 F.3d 235, 241–43 (3d Cir. 2017) (citing *In re Harman Int'l Indus., Inc. Sec. Litig.*, 791 F.3d 90, 103–104 (D.C. Cir. 2015); *Berson v. Applied Signal Tech., Inc.*, 527 F.3d 982 (9th Cir. 2008)); *see also Endo Int'l*, 351 F. Supp. 3d at 902 (qualified cautionary statements considered in the context of actual known data showing adverse information are actionable). For example, Defendants generically warned that "[b]ecause the results of preclinical studies and earlier clinical trials are not necessarily predictive of future results, Zygel may not have favorable results in our planned clinical trials." ¶ 31. However, when making that statement, Defendants already knew that the child and adolescent patients in the BELIEVE 1 trial suffered unfavorable safety results. Defendants were aware, but nevertheless withheld, that virtually all participants in the BELIEVE 1 clinical trial had suffered TEAEs, 60% had suffered TRAEs, and over 20% SAEs. The materialization of actual adverse safety and tolerance data in children rendered Defendants' risk warnings relating to clinical trials inaccurate and misleading. As such, Defendants were duty-bound to disclose the adverse safety data from the BELIEVE 1 clinical trial.

Defendants' also disregard that in this Circuit, registrants have a duty to update. *Burlington*, 114 F.3d at 1431. Even if a statement is true when made, when subsequent events "that could *fundamentally change* the natures of the companies involved" render it misleading, registrants are duty-bound to disclose the truth. *Id.* (emphasis in original). Zygel is Zynerba's only drug under development. The Company has no approved drugs on the market, and thus no means of generating revenue. Therefore, as Defendants observed the overwhelming numbers of adverse events suffered by their young trial participants, they had a duty to update their prior statements

regarding Zygel's safety. The results of the BELIEVE 1 trial, therefore, "could fundamentally change" the fate of the Company, given that the *Company's* success or failure depends wholly on *Zygel's* success or failure. With other CBD treatments already on the market, and Defendants' claim that Zygel's advantage over those alternatives is its lower incidence of side effects stemming from its transdermal delivery, the fact that their transdermal treatment caused so many side effects during the BELIEVE 1 trial required Defendants to update their statements. Yet throughout the Class Period, Defendants chose to discuss only Zygel's positive clinical safety and toleration results, remaining silent on the prevalence and severity of Zygel's adverse events. ¶¶ 26, 42; Chen Decl. Exs. 1, 2; Defs.' Exs. C, D.

The facts in *Oran*, as relied upon by Defendants, are therefore distinguishable. Defs.' Br. at 29. The *Oran* court concluded that the defendant did not have an affirmative duty to disclose adverse events data suggesting a link between the drug and heart valve disorders because the defendant drug company had not made statements about the safety of its product to investors, instead speaking only about the FDA process generally, and thus had not put the subject of safety "in play." 226 F.3d at 283–85. Here, however, Defendants affirmatively stated that Zygel "result(s) in a lower incidence of gastrointestinal side effects…" and that "transdermal delivery of Zygel avoids the gastrointestinal tract and potential degradation to THC in stomach acid, which should minimize the risk of negative psychoactive effects," thus clearly putting the subject of safety "in play." ¶¶ 17, 26. This triggered Defendants' affirmative duty to fully inform investors regarding the high rates of adverse events, including a 20% SAE rate, that occurred during clinical testing.

Defendants assert that no duty obligated them to speak about the prevalence and severity of Zygel's adverse safety issues because they repeatedly stated that the Company did not plan to

release data about the safety or efficacy from the BELIEVE 1 trial until the third quarter of 2019, and this was consistent with Zynerba's prior standard practice. Defs.' Br. at 8-9, 27-28. Zynerba's previous practice of waiting until a few months after the conclusion of Phase 2 trials to make announcements are distinguishable from the Phase 2 BELIEVE 1 trial at issue. Zynerba's previous clinical trials had ***no*** serious adverse events or treatment-related serious adverse events related to Zygel itself. *See* Defs.' Ex. A, at 11-17. By contrast, ***96%*** of the patients treated with Zygel in the BELIEVE 1 trial suffered TEAEs, ***60%*** suffered TRAEs, and ***20%*** suffered SAEs. If the Company did not want to divulge the safety results until after the BELIEVE 1 trail concluded, they should not have opted to speak about the safety of the drug at all until that time. Defendants' citation to *Huang v. Avalanche Biotechnologies, Inc.*, No. 15-CV-03185-JD, 2016 WL 6524401 (N.D. Cal. Nov. 3, 2016), is therefore inapposite. Defs.' Br. at 27-28. Defendants' previous practices provide no shield against their liability for failure to disclose, given their affirmative statements regarding Zygel's side effects during the Class Period.

Similarly, relying on three SEC filings filed after the Class Period, Defendants argue that Plaintiffs misinterpret the adverse safety results from the BELIEVE 1 clinical trial, asserting that the Company is still pursuing Zygel's approval and commercialization. Defs.' Br. at 12. Not only may the Court not take as true the statements in those exhibits, *see Oran*, 226 F.3d at 289 (courts may take judicial notice of SEC filings only to determine what those documents stated, not for their truth), but two of them post-date the Class Period. Moreover, the Court should not consider Defendants' self- serving interpretations of trial data, contained in documents drafted by Defendants, and filed with the SEC right before Defendants filed their motion to dismiss here. The correct interpretation of the data is a question of fact that is inappropriate for resolution at this stage, when the Court must take all well-pleaded allegations as true.

Moreover, it is well established that "[s]ecurities laws approach matters from an *ex ante* perspective." *Burlington*, 114 F.3d at 1429 n.16; *see also Vivendi*, 838 F.3d at 262 ("[f]raud depends on the state of events when a statement is made, not on what happens later") (*quoting Schleicher v. Wendt*, 618 F.3d 679, 684 (7th Cir. 2010), and *citing Pommer v. Medtest Corp.*, 961 F.2d 620 (7th Cir. 1992)).[10] Just as Plaintiffs cannot plead "fraud by hindsight," Defendants may not exculpate by hindsight. That Zynerba continues to develop Zygel and may ultimately receive FDA approval and commercialize its only therapy under development is irrelevant to whether the adverse safety data existed during the Class Period and Defendants were duty-bound to disclose that data.[11]

For the foregoing reasons, Defendants had a duty to disclose the adverse safety data so as not to mislead investors with their Class Period statements.

2. SEC Reg. S-K, Item 303 Created a Duty to Disclose

Companies must disclose adverse information if required by SEC regulation. Item 303 of Regulation S-K demands disclosure of events and uncertainties that are known to management and reasonably likely to have a material impact on a company's operations. 17 C.F.R. § 229.303. The Third Circuit in *Oran*, 226 F.3d at 275 suggests that Item 303 can give rise to a material 10b–5 omission if the omission is material under *Basic Inc. v. Levinson*, 485 U.S. 224 (1988), and the

[10] In *Pommer*, the Seventh Circuit wrote, "[t]he securities laws approach matters from an *ex ante* perspective: just as a statement true when made does not become fraudulent because things unexpectedly go wrong," the Seventh Circuit continued, "so a statement materially false when made does not become acceptable because it happens to come true. Good fortune ... does not make the falsehood any the less material." 961 F.2d at 623 (citations omitted).

[11] Indeed, though Zynerba concluded the BELIEVE 1 trial in mid-2019, it has not announced a Phase III trial or any other progress in the development of the drug for the treatment of DEE in children and adolescents.

other elements of Rule 10b–5 have been established.[12] As argued herein, Plaintiffs adequately allege actionable misleading statements and scienter. Defendants do not contest materiality or any other elements of the claim.

The high rate of side effects during the BELIEVE 1 trial, including a 20% SAE rate, constituted events and uncertainties with a reasonable likelihood of impact upon the Company's operations. Zynerba has one product—Zygel. It has no product revenue and touts a lower incidence of side effects as Zygel's competitive advantage. Defendants have made clear that Zynerba's very survival hinges on achieving FDA approval and successful commercialization of Zygel. A trend of adverse *safety* events that impacted almost every trial participant treated with Zygel, and which could have prompted a negative FDA action, triggered a duty to disclose under Item 303. *See Silverstrand Investments v. AMAG Pharm., Inc.*, 707 F.3d 95, 99 (1st Cir. 2013) (the company had the duty under Item 303 to disclose the risk that 23 post-marketing SAEs could have prompted FDA action).

3. Zynerba's Open Market Sales During the Class Period Triggered a Duty to Disclose

Courts impose a duty to disclose on defendants that engage in insider trading to ensure that corporate insiders will not benefit personally through fraudulent use of material, nonpublic information. Insiders must disclose material facts which are known to them by virtue of their position, but which are not known to persons with whom they deal and which, if known, would

[12] [12] The Second Circuit in *Stratte-McClure v. Morgan Stanley*, 776 F.3d 94 (2d Cir. 2015), interprets the Third Circuit decision in *Oran* as holding "that in certain instances a violation of Item 303 *could* give rise to a material 10b–5 omission. At a minimum, *Oran* is consistent with our decision that failure to comply with Item 303 in a Form 10–Q can give rise to liability under Rule 10b–5 so long as the omission is material under *Basic,* and the other elements of Rule 10b–5 have been established." *Id.* at 103–04.

affect their investment judgment. 15 U.S.C. § 78t-1(a).[13] This doctrine, known as the "abstain or disclose" rule, has been found to apply equally to individual insiders and corporate issuers engaging in a public offering of securities. *See In re Thornburg Mortg., Inc. Sec. Litig.*, 824 F. Supp. 2d 1214, 1246–47 (D.N.M. 2011), *aff'd sub nom. Slater v. A.G. Edwards & Sons, Inc.*, 719 F.3d 1190 (10th Cir. 2013).[14]

Here, Defendants omitted material adverse information regarding Zygel and the BELIEVE 1 trial from statements they issued during the Class Period. While in possession of this material adverse safety data, Defendants caused Zynerba to sell 2,082,031 shares of common stock in the open market under an Open Market Sales Agreement with Jefferies LLC ("Jefferies Agreement"), earning Zynerba $27 million in net proceeds. ¶ 39. That is precisely the type of conduct the insider trading prohibitions are designed to prevent. The open market sales pursuant to the Jefferies Agreement coincided with the late stages of the BELIEVE 1 trial, indicating that Defendants had accumulated most if not all the adverse safety data. Defendants therefore had a duty to disclose

[13] The Exchange Act defines "person" as "a natural person, company, government or political subdivision, agency, or instrumentality of government." 15 U.S.C. § 78c(a)(9). In addition, Section 20(a) of the Exchange Act imposes control person liability on control persons of insider traders. 15 U.S.C. § 78t-1(b)(3). As such, not only can Zynerba be guilty of insider sales, but the Individual Defendants can be liable for those violations as control persons.

[14] Citing *Shaw v. Digital Equip. Corp.*, 82 F.3d 1194, 1204 (1st Cir. 1996) (stating that, if corporate issuers of stock were not subject to liability under the insider-trading law, "a corporate issuer selling its own securities would be left free to exploit its informational trading advantage, at the expense of investors, by delaying disclosure of material nonpublic negative news until after completion of the offering."), *superseded by statute on other grounds*, 15 U.S.C. § 78u4(b)(l)-(2); *McCormick v. Fund Am. Companies, Inc.*, 26 F.3d 869, 876 (9th Cir. 1994) ("Numerous authorities have held or otherwise stated that the corporate issuer in possession of material nonpublic information, must, like other insiders in the same situation, disclose that information to its shareholders or refrain from trading with them.") (citations omitted); *Kohler v. Kohler Co.*, 319 F.2d 634, 638 (7th Cir. 1963) ("[U]nderlying principles [regarding disclosure of material nonpublic information] apply not only to majority stockholders of corporations and corporate insiders, but equally to corporations themselves"); *Green v. Hamilton Int'l Corp.*, 437 F. Supp. 723, 728 (S.D.N.Y. 1977) ("[T]here can be no doubt that the prohibition against 'insider' trading extends to a corporation.")

this material, adverse, non-public information in their possession about the staggering numbers of safety events during the BELIEVE 1 clinical trial while selling their stock on the open market. Their failure to disclose that information is actionable.[15]

C. The Statements Then-Existing SAEs Rendered False are Not Inactionable Puffery

Defendants incorrectly assert that certain of their false and misleading statements are inactionable puffery or mere "interpretations of the results of preclinical trials." Defs.' Br. at 30-31. They are incorrect. While vague expressions of hope and cautiously optimistic statements expressing hope for a positive result are inactionable puffery, *Burlington*, 114 F.3d at 1427-28, materially misleading statements regarding facts that are concrete and verifiable are actionable. *See Urban Outfitters*, 103 F. Supp. 3d at 651 (denying motion to dismiss, holding that defendants' misrepresentations regarding the company's strong sales trends and decreased markdowns are not puffery, because they provide 'concrete information about the performance [and business practice] of [a] specific' brand") (citation omitted); *see also In re ATI Techs., Inc. Sec. Litig.*, 216 F. Supp. 2d 418, 436 (E.D. Pa. 2002) ("[d]efendants' statements that [the demand for the Rage chips as 'solid,' 'strong,' and 'good,'] were not puffery, but provided investors with concrete information about the performance of specific products"). More, with respect to opinions or "interpretations," reasonable investors expect that the speakers have a factual basis upon which to base their opinion. If there is no factual basis, or available facts bely the opinion, then the opinion can be actionable. *Omnicare*, 575 U.S. at 188-89 ("a reasonable investor may, depending on the

[15] Defendants do not address Zynerba's open market sales in their Motion, much less argue that they do not trigger a duty to disclose. They are therefore foreclosed from raising it in their Reply. *Anspach ex rel. Anspach v. City of Philadelphia, Dep't of Pub. Health*, 503 F.3d 256, 258 n.1 (3d Cir. 2007) (absent compelling circumstances, "failure to raise an argument in one's opening brief waives it"); *Bayer AG v. Schein Pharm. Inc.*, 129 F. Supp. 2d 705, 716 (D.N.J. 2001) ("It is axiomatic that reply briefs should respond to the respondent's arguments or explain a position in the initial brief that the respondent has refuted"), *aff'd,* 301 F.3d 1306 (Fed. Cir. 2002).

circumstances, understand an opinion statement to convey facts about how the speaker has formed the opinion—or, otherwise put, about the speaker's basis for holding that view").

Defendants assert that the statement on Zynerba's website regarding the lower incidence of gastrointestinal side effects is puffery because they prefaced an objectively verifiable fact—Zygel causes fewer gastrointestinal issues than oral CBD therapies—with the title "potential benefit." Def. Br. 31. Their assertion is objectively untrue. The paragraph describing the lower incidence of gastrointestinal side effects does not state that there is a *potential* for lower incidence. It states that given its transdermal delivery, Zygel "result[s] in a lower incidence of gastrointestinal side effects." ¶ 26. No qualifier. The "potential benefit" title preceding that paragraph, refers to its statements that the transdermal delivery "potentially enables lower dosage levels" and "may include fewer drug-drug interactions," not the lower incidence of side effects. The objectively verifiable fact relates to patients' safety and tolerance of Zygel—fewer gastrointestinal side effects.

Raising the subject of Zygel's side effects required Defendants to disclose in the context of those statements that with respect to safety and tolerance, the BELIEVE 1 clinical trial uncovered that 90% of children experienced TEAEs, 60% experienced TRAEs and over 20% experienced SAEs. The safety and tolerance information from the clinical trial, therefore, belies Defendants' statements of better tolerance and safety. Defendants' statements about safety as Zygel's competitive advantage over oral CBD were not vague statements of optimism in the face of then-existing, objectively verifiable facts that almost all the children and adolescents treated with Zygel suffered adverse events, and over 20% suffered SAEs.

Defendants' argument that their statements in the 2018 10-K (*see* ¶ 30) are inactionable opinion also fails. The Complaint alleges that Defendants claimed to believe that Zygel may provide an effective treatment for epilepsy and that specialists and patients are interested in its

potential, especially for children with DEE. ¶ 30. They said this, knowing that children did not tolerate Zygel well, with 90% TEAEs, 60% TRAEs, and over 20% SAEs. The Complaint, therefore, pleads specific, material, adverse facts that undermine Defendants' opinion, rendering that opinion actionable. *Omnicare*, 575 U.S. at 194 (complaint "must identify particular . . . facts going to the basis for the issuer's opinion[,] . . . whose omission makes the opinion statement at issue misleading to a reasonable person reading the statement fairly and in context"); *see also In re Int'l Bus. Machines Corp. Sec. Litig.*, 163 F.3d 102, 107 (2d Cir. 1998); *Herskowitz v. Nutri/Sys., Inc.*, 857 F.2d 179, 184 (3d Cir. 1988) (an opinion or projection, like any other representation, will be deemed untrue for purposes of the federal securities laws if it is issued without reasonable genuine belief or if it has no basis).

Endo International is directly on point. In that case, the defendants extolled the crush-resistant formulation of an opioid while withholding that intravenous abuse had increased. 351 F. Supp. 3d at 910-11. Judge Savage held that while Defendants' statements about the virtues of the new formulation of their opioid may have been opinions, the underlying facts belying those opinions rendered them actionable. *Id.* Similarly, here, Defendants' statements are actionable because the underlying facts known to them belied their public misstatements.

D. Defendants Are Not Entitled to Safe Harbor Protection

To receive protection from the statutory safe harbor or "bespeaks caution" doctrine, a forward-looking statement must be "accompanied by meaningful cautionary statements." 15 U.S.C. § 78u-5(c)(1)(A)(i). "[T]the bespeaks caution doctrine is only available for forward-looking statements, and cannot be invoked for misleading statements of existing fact." *In re Cell Pathways, Inc.*, No. 99-725, 2000 WL 805221, at *11 (E.D. Pa. June 20, 2000). "[T]o warn that the untoward may occur when the event is contingent is prudent; to caution that it is only possible for the

unfavorable events to happen when they have already occurred is deceit." *In re Westinghouse Sec. Litig.*, 90 F.3d 696, 710 (3d Cir. 1996) (quoting *Rubinstein v. Collins*, 20 F.3d 160, 171 (5th Cir. 1994)).

Defendants allege that they made extensive, specific risk disclosures concerning the risks of potential setbacks in Zygel's clinical trials, that the drug would never obtain FDA approval, and that the drug might never be commercialized. Defs.' Br. at 9-11, 32-33. This is not true. As the Complaint allege, these generic risk warnings describing potential risks facing Zynerba such as "Zygel may not have favorable results in our planned clinical trials," "failures or delays in our clinical trials of Zygel could result in increased costs …," "regulatory approval processes of the FDA … are ... inherently unpredictable," were false and misleading because these statements portrayed these risks as purely hypothetical though they had in fact already materialized in the BELIEVE 1 trial. ¶¶ 31, 35, 38. As detailed above, the Complaint alleges contemporaneous facts supporting the inference that these risks had already materialized at the time the statements were made. *See supra*. Thus, Defendants' purported cautionary language was itself misleading considering historical fact, and such language cannot insulate from liability the failure to disclose that the risk has transpired. *See In re MobileMedia Sec. Litig.*, 28 F. Supp. 2d 901, 928 (D.N.J. 1998) (holding that warnings of a mere contingency when the contingency had already occurred were insufficient to warrant the application of either the safe harbor or the bespeaks caution doctrine). Indeed, statements regarding the unpredictability of the FDA approval process are common to all pharmaceutical companies and hardly meaningful in the face of undisclosed known risks to that process. *See Yanek v. Staar Surgical Co.*, 388 F. Supp. 2d 1110, 1123 (C.D. Cal. 2005) (generic language like FDA "approval is never certain" is not meaningful and applies to "literally

any issuer subject to FDA regulation"); *accord In re MannKind Sec. Actions*, 835 F. Supp. 2d 797, 817 (C.D. Cal. 2011).

Furthermore, in order for a forward-looking statement to fall within the protection of the bespeaks caution doctrine, the cautionary statements "must be substantive and tailored to the specific future projections, estimates or opinions in the prospectus which the plaintiffs challenge." *In re MobileMedia,* 28 F. Supp. 2d at 928. Zynerba's cautionary language that it "has "incurred significant losses … and … will continue to incur losses," and "currently ha[s] no commercial revenue," Defs.' Br. at 9-10, are just boilerplate disclaimers not directly tailored to the misleading statements that Plaintiffs allege. *See supra*. "[V]ague or blanket (boilerplate) disclaimer[s] which merely warn[] the reader that the investment has risks will ordinarily be inadequate to prevent misinformation." *In re Donald J. Trump,* 7 F.3d at 371.

E. The Complaint Adequately Pleads that Defendants Acted with Requisite Fraudulent Intent

To plead scienter, a complaint must allege facts giving rise to a strong inference of "either reckless or conscious behavior." *See Institutional Inv'rs Grp. v. Avaya, Inc.*, 564 F.3d 242, 276 (3d Cir. 2009) (citations omitted).[16] Recklessness, the Third Circuit has established, "involve[es] not merely simple, or even inexcusable negligence, but an extreme departure from the standards of ordinary care, and which presents a danger of misleading buyers or sellers that is either known to the defendant or is so obvious that the actor must have been aware of it." *Id*. at 267 n.42. "[S]ecurities fraud claims typically have sufficed to state a claim based on recklessness when they

[16] Misquoting *In re AstraZeneca Securities Litigation*, 559 F. Supp. 2d 453, 471 (S.D.N.Y. 2008), Defendants suggest that this Court can find scienter only from facts "indicat[ing] that defendants knew that the statements were false or misleading." Defs.' Br. at 25. The complete quotation from *AstraZeneca* reads, "[t]here is no allegation of any "red flag" or anything else to indicate that defendants knew that the statements were false or misleading ***or that defendants were recklessly issuing false or misleading information to the public***." 559 F. Supp. 2d at 471 (emphasis added).

have specifically alleged defendants' knowledge of facts *or access to information* contradicting their public statements. Under such circumstances, defendants knew or, *more importantly, should have known* that they were misrepresenting material facts related to the corporation." *In re Innocoll,* 2020 WL 1479128, at *12 (citations omitted) (emphases in original). "It is unnecessary to read in an additional requirement that Plaintiffs must explicitly plead that Defendants examined or considered the information available to them." *Id.*[17]

To evaluate the sufficiency of the Complaint's scienter allegations, the Court will determine "whether *all* of the facts alleged, taken collectively, give rise to a strong inference of scienter, not whether any individual allegation, scrutinized in isolation, meets that standard." *Tellabs*, 551 U.S. at 310, 322-23 (emphasis in original). An inference of scienter is "strong" if it is "*at least as likely as* any plausible opposing inference." *Id.* at 324, 328 (emphasis in original). The inference of scienter need not be more likely than a plausible opposing inference; in such an instance, the tie goes to the plaintiff. *Id.* at 324. Also, "[t]he inference that the defendant acted with scienter need not be irrefutable, *i.e.*, of the 'smoking gun' genre, or even the 'most plausible of competing inferences.'" *Id.* (citation omitted). Indeed, scienter can be inferred from "circumstantial evidence." *Burlington*, 114 F.3d at 1418. "The absence of a motive allegation, though relevant, is not dispositive." *Matrixx,* 563 U.S. at 48.

1. The Complaint Sufficiently Pleads Defendants' Recklessness

There is no dispute that Zygel is of central importance to Zynerba, given that the Company has no other products in its pipeline and no products generating revenue. ¶¶ 2-3. Indeed, Defendants have stated that Zygel is its "lead asset." ¶ 19. The "core operations doctrine," which the Third Circuit has adopted, provides that a complaint sufficiently pleads defendant's fraudulent

[17] Defendants' assertion that the Complaint must plead actual knowledge thus fails. Defs.' Br. at 15.

intent where that defendant misrepresented or omitted a material fact related to "core matters of central importance to the company and its high-level executives." *Urban Outfitters*, 103 F. Supp. 3d at 653–54 (finding scienter where operation consisted of 44% of the whole and misstatements related to sales declines in those operations) (quotations omitted); *see also Endo Int'l,* 351 F. Supp. 3d at 906 (finding strong inference of scienter for individual defendants where the drug at issue was the "primary product" and the second-largest revenue source of the company); *see also Emps.' Ret. Sys. of P.R. Elec. Power Auth. v. Conduent Inc.,* No. 19-8237 (SDW) (SCM), 2020 WL 3026536, at *8 (D.N.J. June 5, 2020) (finding strong inference of scienter based on individual defendants' identification of the tolling operations as a "core" business segment); *In re Navient Corp. Sec. Litig.*, No. CV 17-8373 (RBK/AMD), 2019 WL 7288881, at *11 (D.N.J. Dec. 30, 2019) (finding the core operation inference applicable as education-related revenue at issue comprised 82.8% of the company's total revenue). Zygel was not ***a*** core operation of Zynerba, it was ***the*** core operation. With other CBD treatments available on the market, Defendants identified fewer side effects as Zygel's competitive advantage. As such, Defendants were singularly focused on the clinical trials to determine Zygel's safety and efficacy.

Moreover, the BELIEVE 1 clinical trial was the first in which Zynerba assessed the safety and efficacy of Zygel in children and adolescents and which specifically focused on treatment of DEE. Defendants, themselves referred to the period that the BELIEVE 1 clinical trial ushered it as "transformational."[18] The most reasonable inference, indeed the only reasonably inference, is

[18] In Zynerba's May 8, 2019 press release, disclosing "operational highlights" from the period ended March 31, 2019, Defendant Anido stated:

> We are entering a ***transformational period for Zynerba during which we expect top line data from four neuropsychiatric disorder trials with Zygel***™, our patent protected CBD gel.

Defs.' Ex. B, at 1 (Emphasis added).

that Defendants assiduously focused in real time on the data emerging from the BELIEVE 1 clinical trial.

In addition to pleading facts demonstrating that Zygel is the Company's core, and only, operation, the Complaint pleads additional facts "connecting the executives' positions to their knowledge." *In re Delcath Sys., Inc. Sec. Litig.*, 36 F. Supp. 3d 320, 335 (S.D.N.Y. 2014) (citations omitted). During the Class Period, Zynerba had approximately 25 full-time employees, including Defendants Anido and Fickenscher. ¶ 20. The small size of a pharmaceutical company like Zynerba has been found to contribute to the compelling inference of scienter. *See In re Delcath Sys., Inc. Sec. Litig.*, 36 F. Supp. 3d 320, 335 (S.D.N.Y. 2014) (finding Delcath's headcount, which ranged from 17-80 employees during the class period, indicative of scienter). As CEO and CFO of such a small company with one key product and no other approved products on the market, the most compelling inference is that Defendants Anido and Fickenscher knew about the adverse safety events occurring in vast numbers during the BELIEVE 1 trial. 21 C.F.R. § 312.32(b) Additionally, this is not the first time Defendant Anido has gone through the FDA approval process with a pharmaceutical company. With his 35-year history leading other specialty pharmaceutical companies in their efforts to achieve regulatory approval and commercialize therapies,[19] and his statements regarding the Phase 2 process for Zygel as "transformational," Defendant Anido clearly knew the significance the results of the BELIEVE 1 trial would have on Zygel's prospects for

[19] In Zynerba's Proxy Statement on Form 14A, filed with the SEC on April 25, 2019, the Company boasted that Defendant Anido possessed "more than 35 years of executive, operational and commercial leadership experience in the pharmaceutical industry." For example, the Company stated, as CEO of specialty pharmaceutical company NuPathe, Defendant Anido, "led the company through . . . FDA[] approval of its lead product Zecuity®, a transdermal patch for migraines." Before NuPathe, as CEO of specialty pharmaceutical company Auxilium, Defendant Anido "led the company in its commercialization of its lead product, Testim®, a testosterone gel" and "through the FDA approval and commercialization of Xiaflex®, an injectable collagenase for Dupuytren's Contracture."

approval and commercialization. The only logical inference is that Defendant Anido kept apprised of those results.

Defendants' arguments suggest this Court should view a clinical trial like a Ronco rotisserie oven, "set it and forget it." As Defendants well knew based on their experience[20] and job descriptions, FDA regulations did not allow them to "set it and forget it." Aside from the common sense inference that they paid attention to the trial simply given its criticality to the Company's survival, FDA regulations required them to closely monitor the progress and results of the BELIEVE 1 clinical trial. For investigational new drugs ("IND") like Zygel, the FDA required that Zynerba "promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor . . . , including information derived from any clinical or epidemiological investigations . . . ." 21 C.F.R. §312.32(b). Not only did FDA regulations require Defendants to review safety information, but they mandated, "[t]he sponsor must notify FDA and all participating investigators . . . in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting" as, among other things, a serious event. ¶ 22; 21 C.F.R. § 312.32(c)(1).[21]

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[20] Like Defendant Anido, Zynerba's Proxy Statement on Form 14A, filed with the SEC on April 25, 2019, describes Defendant Fickenscher as a veteran of specialty pharmaceutical companies with "more than 30 years of financial, business development and executive leadership experience in the pharmaceutical industry," including from 2014 to 2016 as CFO of specialty pharmaceutical company, Antares Pharma, Inc., and from 2005 to 2014 as CFO of specialty biopharmaceutical company, Auxilium Pharmaceuticals, Inc.

[21] Defendants incorrectly preface SAE with "unexpected" in relation to their FDA reporting obligations. Defs.' Br. at 21-22. The regulation does not qualify the reporting requirements for SAEs with the word "unexpected," 21 C.F.R. § 312.32 (c). *Koncelik v. Savient Pharm., Inc.*, No. 08 CIV. 10262 GBD, 2010 WL 3910307, at *8 (S.D.N.Y. Sept. 29, 2010), *aff'd,* 448 F. App'x 154 (2d Cir. 2012) is distinguishable because the cardiovascular SAEs experienced in the *Savient* trial are exactly the underlying prior cardiovascular diseases that these patients had already had before they entered the trial; the Savient drug was aimed at curing underlying prior cardiovascular

In its *Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies* (Dec. 2012), the FDA elaborated on its requirement that pharmaceutical companies such as Zynerba establish proper surveillance for ongoing clinical trials. In relevant part, that FDA Guidance states, "[b]ecause it is critical that a drug product's risks be adequately assessed during development, sponsors should ensure that they have in place a systematic approach for safety surveillance." The FDA Guidance continued, "[s]uch an approach should include a process for ***reviewing, evaluating, and managing*** accumulating safety data from the entire clinical trial database at appropriate intervals."[22]

Additionally, among the responsibilities of sponsors for INDs like Zynerba, however, is "ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug." 21 C.F.R. § 312.50. In addition, "[t]he sponsor shall monitor the progress of all clinical investigations being conducted under its IND . . . . [and] review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator," reporting those safety results to the FDA pursuant to § 312.32. 21 C.F.R. §

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diseases. In *Savient*, FDA recognized "[t]he occurrence of these events [as] not unexpected given the high prevalence of underlying cardiovascular disease in the patient population who participated in these trials." *Id.* at 8. But here, the SAEs suffered ***during treatment*** are ***not*** symptoms of DEE. Defendants cannot negate the compelling inference of scienter by reference to their own self-serving post-Class Period statement in Zynerba's 2019 Form10-K Annual Report, dated March 10, 2020, that children with DEE are medically fragile and expected to suffer health issues—a claim which did not appear in any prior disclosure regarding the results of the BELIEVE 1 trial. Defs.' Br. 21-22. Moreover, there is nothing in the record to suggest that children and adolescents with DEE are expected to suffer the precise types of adverse events they suffered while treated with Zygel. In any event, even if this Court takes judicial notice of the 10-K, it cannot do so for the truth of the matters asserted therein. *See Oran*, 226 F.3d at 289.

[22] https://www.fda.gov/media/79394/download; *see also* FDA, *Guidance for Clinical Trial Sponsors*, at 3 (Mar. 2006) ("All clinical trials require safety monitoring"), https://www.fda.gov/media/75398/download (last accessed June 10, 2020).

312.56(a), (c). To comply with their FDA reporting obligations, therefore, the most reasonable inference is that Defendants monitored adverse events during the BELIEVE 1 trial.

Unlike the evaluation of efficacy which cannot be done until the trial's completion, adverse events occur in real time and the FDA regulations required Zynerba to timely report them under the circumstances present in this case. To that end, the Complaint alleges that Defendants had access to a safety database that Zynerba maintained, where all safety events were promptly entered. ¶ 23. Additionally, the BELIEVE 1 trial was open label—not blind. That means, Defendants knew which trial participants received the drug and which suffered safety events when they occurred. *Id.* Defendants thus had access (unsurprisingly given their obligations under FDA regulations) to the adverse safety data omitted from their public misstatements. *In re Innocoll*, 2020 WL 1479128, at *12. Thus, the most cogent and compelling inference is that Defendants either knew of the safety data virtually in real time or ignored the safety data, rendering them reckless. Either way, the Complaint sufficiently pleads a strong inference of scienter. *Avaya*, 564 F.3d at 271 ("perceived importance" of the issue in question "supports an inference that" senior officers "p[aid] close attention to these numbers").

Defendants improperly rely on *Oran* and *In re Advanta Corp. Securities Litigation*, 180 F.3d 525 (3d Cir. 1999) to argue that the Complaint insufficiently alleges Individual Defendants' scienter based *solely* on their job titles and their signatures in SEC filings. Defs.' Br. at 19-20.[23] It is correct that generalized imputations of knowledge based solely on individual defendants'

[23] *In re Radian Securities Litigation*, 612 F. Supp. 2d 594, 620 (E.D. Pa. 2009), does not support Defendants' argument. *Radian* ruled that signing SOX certifications *alone* does not establish scienter. However, the *Radian* court also ruled that signing SOX certifications supports an inference of scienter if "something more" is alleged, as is the case here. *See also Garfield v. NDC Health Corp.,* 466 F.3d 1255, 1265-66 (11th Cir.2006) (finding a SOX certification probative of scienter if plaintiffs show that the person signing the certification was "severely reckless" in certifying the accuracy of its financial statements).

positions do not suffice. But the *Advanta* court, analyzing *In re Ancor Communications, Inc. Securities Litigation,* 22 F. Supp. 2d 999 (D. Minn. 1998), further explains that facts demonstrating that an important transaction "was undeniably the most significant contract [to the defendant company] [ ] support[s] an unusually strong inference of scienter." *In re Advanta*, 180 F.3d at 539. Here, the Complaint does not simply allege the Individual Defendants' positions, but also that Zygel is Zynerba's core, *i.e.,* "most significant," operation and further alleges the Individual Defendants' access to the undisclosed safety data when issuing their misleading statements.

Still further, the sheer magnitude of adverse events that trial participants suffered during BELIEVE 1 clinical testing of Zynerba's core product supports a strong inference of scienter. In *Avaya*, the Third Circuit found that the magnitude of an adverse condition—pricing discounts causing margin contraction in that case—coupled with its importance to the registrant's financial condition or operations, can support of a strong inference of fraudulent intent. 564 F.3d at 270-71 (when the defendants made allegedly false statements about pricing, margins, a "central question" for investors, "were significantly contracting" against the annual projection and the prior quarter).

The magnitude here is indisputable. Ten out of forty-eight trial participants suffered SAEs, a material 20%. The magnitude of adverse safety events, and SAEs in particular, is especially noteworthy given that in prior Phase I testing, Zynerba reported that Zygel was safe and well-tolerated for adults, with adverse events experienced at the same rate as those treated with placebo. Defs.' Ex. A, at 17. In the BELIEVE 1 clinical trial, however, the rate at which patients *treated with Zygel* suffered adverse safety events—90% TEAE, 60% TRAE, 21% SAE—renders any competing inference about Defendants' reckless disregard of this adverse information less cogent and compelling.

Considering the foregoing facts, it is unsurprising that Defendants do not bother offering a competing inference suggesting that they did not know in real time of the massive numbers of adverse safety events. Instead, Defendants seemingly concede their knowledge of the adverse safety data but argue that they "did not disclose the adverse events because the BELIEVE 1 trial was ongoing," and they stated that they would wait until all results were in to analyze the safety and efficacy. Defs.' Br. at 23. That is not a cogent and compelling counter-inference. It is an excuse. This "duty to disclose" argument, disguised as a scienter argument, is unavailing for the reasons stated above. The most compelling inference is that Defendants knowingly or recklessly withheld material safety information regarding which they had actual, real-time knowledge.

Rather than disclaim knowledge, Defendants claim that it is "entirely plausible that they did not believe the events were alarming or significant given the broad definition of adverse events, the medically fragile nature of children suffering from DEE and participating in the trial, and the six-month length of the study." Defs.' Br. at 23. In so arguing, Defendants mistakenly assume they need only offer an inference that is "entirely plausible," though in fact their competing inference must be cogent and more compelling than that alleged in the Complaint to negate scienter. *In re Columbia Labs., Inc., Sec. Litig.*, 602 F. App'x 80, 84 (3d Cir. 2015) They fail to do so. Additionally, Defendants' assertion as to the significance of the safety data is a materiality argument for summary judgment and trial, not a defense against the sufficiency of the Complaint's scienter allegations. [24]

[24] Defendants cases are inapposite and distinguishable. *In re Human Genome Scis. Inc. Sec. Litig.*, 933 F. Supp. 2d 751, 761 (D. Md. 2013) (defendants did not give the public misleading information regarding the trial as they never spoke about the trial except three passing references to a nameless trial that is possibly the study at issue); *In re Columbia Labs., Inc. Sec. Litig.*, 602 F. App'x 80, 84 (3d Cir. 2015) (no intent to deceive, manipulate, or defraud investors because the underlying statements were not misleading.). The allegations in *In re Sanofi Securities Litigation*, 87 F. Supp. 3d 510, 544 (S.D.N.Y. 2015), are fundamentally different from the allegations in the Complaint.

In any event, even if the safety and tolerance data Defendants received and reviewed did not alarm them, that in no way absolves them for failing to disclose the adverse information during the Class Period. At the March 11, 2019 commencement of the Class Period, the BELIEVE 1 clinical trial was already half-over. As such, and given the staggering percentage of trial participants that suffered safety events, it is reasonable to infer that participants had already manifested material SAEs, TEAEs, and TRAEs by that time. At the time Defendants omitted the BELIEVE 1 clinical trial "top line" results from their May, June, and August 2019 statements, they knew that most trial patients had suffered adverse events and a material amount suffered SAEs. Their culpability cannot rest on their ultimate opinion about whether a particular participant's suffering alarmed them. The fact is that by no later than early May 2019, Defendants knew that the raw data, on its face, was less favorable than previous clinical trial results by an order of magnitude that required a disclosure, particularly given statements on Zynerba's website raising the topic of side effects, and given that this was Zygel's first clinical trial evaluating its safety and efficacy in children. It is therefore at least equally cogent and compelling to infer that Defendants were minimally reckless in failing to disclose the adverse safety data from the BELIEVE 1 trial.

Given Defendants' failure to parry the core operations doctrine as well as their connection and access to the information in question, the Complaint adequately pleads at least an equally cogent and compelling inference that Defendants acted with fraudulent intent.

Here, the prevalence and severity of adverse events that participants in the BELIEVE 1 clinical trial suffered created a duty to disclose when the adverse events occurred in order to make Defendants' historic and present statements not misleading. Plaintiffs do not allege the study design was fatally flawed or the adverse events rendered the drug dead. *Sanofi* is, therefore, inapplicable.

2. The Motive Allegations Bolster the Inference of Scienter

Though motive on its own cannot establish a strong inference of scienter (nor is it required to establish a strong inference of scienter), the motive allegations in the Complaint, when considered holistically with the allegations of scienter described above, strengthen the inference of fraudulent intent. *Avaya*, 564 F.3d at 277-78.

Generally, a development stage drug company's need to raise money to support its clinical trials provides sufficient motive to support a strong inference of fraudulent intent. *Key Equity Inv'rs, Inc. v. Sel-Leb Mktg. Inc.*, 246 F. App'x 780 (3d Cir. 2007) (biotech company's motive to raise money to pay for clinical trials supported scienter); *MannKind*, 835 F. Supp. 2d at 812 (motive to secure financing necessary to pay for core operations supported scienter).[25] As a development-stage biotechnology company that has never had any products generating revenue, Zynerba needed extensive financing to complete the clinical trials and commercialize Zygel. As Defendants stated, "***[w]e will require additional capital to fund our operations and if we fail to obtain necessary financing, we will not be able to complete the development and commercialization of our product candidates***." Defs.' Ex. A, at 41. Alone, these facts suffice as motive, contributing to a strong inference of scienter.

But the allegations of motive go even further. Zynerba sold its own shares into the open market without disclosing the BELIEVE 1 clinical trial raw data that they would ultimately disclose in September 2019. A company selling its own shares into the market while in possession

[25] Defendants do not cite a single case in which the company would face bankruptcy but for a capital raise made possible by the false statements. Rather the two cases that Defendants cite both involve raising capital in the ***ordinary course of business.*** *Klein v. Autek Corp.*, 147 F. App'x 270 (3d Cir. 2005) (no motive for an outside attorney because he attempted to collect attorney fees); *Key Equity Inv'rs, Inc. v. Sel-Leb Mktg. Inc.*, 246 F. App'x 780 (3d Cir. 2007) (no motive because renegotiating credit line was conducted in the ***ordinary course of business (when it was up for renewal***)).

of material, adverse non-public information, constitutes a strong motive, thus bolstering the Complaint's scienter allegations. *In re Thornburg Mortg., Inc. Sec. Litig.*, 695 F. Supp. 2d 1165, 1202 (D.N.M. 2010) (allegations that company sought financing while in possession of the information it omitted "nudge the ball … further toward" scienter); *see also In re Cabletron Sys., Inc.*, 311 F.3d 11, 39 (1st Cir. 2002) (allegations of defendants' "concealment of the serious and worsening deterioration of Cabletron's financial health as a significant motive for the alleged fraud" supported finding of scienter because they were "more than the usual concern by executives to improve financial results; the executives' careers and the very survival of the company were on the line.").[26] Specifically, pursuant to a 2017 Open Market Sales Agreement, Defs.' Ex. F, at 23, the Individual Defendants caused Zynerba to sell 2,082,031 shares of its stock into the open market for net proceeds of over $27 million. ¶ 39. This sale was not a typical offering where Defendants disclosed in advance their intention to sell the stock and, themselves with their bankers, determined the price. Rather, Defendants timed these sales with no advance notification to the market, and accepted market price. Defendants sold these shares while in possession of adverse material raw safety data from the BELIEVE 1 trial. Significantly, Defendants had a choice of when to sell. As of March 31, 2019, Zynerba claimed to have $68.3 million of cash and cash equivalents, Defs.' Ex. B, at 4, and stated that "[m]anagement believes that current cash and cash equivalents are sufficient to fund operations and capital requirements into the first quarter of 2021." Defs.' Ex. B, at 8. Even as Defendants stated that completing approval and commercialization of Zygel would require "substantial additional financings," nothing required them to sell shares to raise $27 million in May 2019 specifically. Given Zynerba's cash position and Defendants' possession of material,

[26] Contrary to Defendants' assertion, Defs.' Br. at 16-18, even if Zynerba's open market sales do not constitute motive—and they do—the absence of motive is not dispositive to this Court's evaluation of the sufficiency of the Complaint's scienter allegations. *Matrixx*, 563 U.S. at 48.

non-public adverse information, Zynerba's sales were suspicious in timing, supporting a strong inference of fraudulent intent.

Defendants' citation to *In re Egalet Corp. Securities Litigation*, 340 F. Supp. 3d 479, 512 (E.D. Pa. 2018), Defs.' Br. at 18, misses the mark. In *Egalet*, Judge Baylson found, in relevant part, that the defendants' SEC filings showed that the individual defendants sold shares to pay the tax liability incurred as a result of restricted shares vesting. *Oran*, 226 F.3d at 290 Those defendants needed that cash, at that time, to satisfy their tax liability. Satisfying a tax liability for vesting shares, at the time they vest, enables an individual to avoid paying the tax authorities using out of pocket cash. Here, however, the need for cash was not acute and immediate.

Rather than a mere "corporate desire to raise capital" as Defendants argue, Def. Br. 18, the timing of the open market sale here suggests that Defendants opted to raise the funds before disclosing material adverse data to the market, knowing they would have difficulty raising the funds when they needed them later to complete clinical testing and commercialize Zygel (assuming they convinced the FDA to grant approval). *Oran*, 226 F.3d at 290. Selling shares to pay a tax liability, an acute and immediate need for cash, is fundamentally different from choosing to sell at the market price when management believes that its cash position at the time of sale is "sufficient to fund operations." Here Defendants chose when to sell, accepting the market price. At the time they caused Zynerba to sell, Defendants knew or recklessly disregarded material adverse data[27] from the BELIEVE 1 trial. The federal securities laws required Defendants to abstain or disclose that material adverse information. *In re Thornburg Mortg., Inc. Sec. Litig.*, 695 F. Supp. 2d at 1209. Zynerba's open market sales while in possession of undisclosed material adverse

[27] *See Oran*, 226 F.3d at 282 (materiality and adverse nature of information is established at the pleading stage if the stock price fell in response to its disclosure).

information and the timing of those sales establish motive and thus contribute to the strong inference of scienter.

Defendants incorrectly cite *Burlington*, 114 F.3d at 1423, to assert that Plaintiffs must allege facts showing that "each individual corporate defendant" had the "motive to commit fraud and an opportunity to do so." Defs.' Br. at 16. This interpretation is wrong. A complaint can adequately allege motive based on corporate or collective scienter to plead an inference of scienter against a corporate defendant without raising the same inferences required to attribute scienter to an individual defendant. *Rahman v. Kid Brands, Inc.*, 736 F.3d 237, 246 (3d Cir. 2013). Moreover, corporations operate through individuals. Even though Defendants Anido and Fickenscher, themselves, did not sell Zynerba shares, as the two most senior officers of Zynerba, they determined the timing of the Company's open market sales while in possession of undisclosed material adverse information.

For those reasons, Zynerba's sales of 2,082,031 shares for net proceeds of $27 million while in possession of material adverse information about its core operation supports at least an equally compelling inference that Defendants omitted the information from the BELIEVE 1 clinical trial with requisite fraudulent intent.

F. The Complaint Adequately Pleads a Section 20(A) Claim

Defendants assert that the Court should dismiss Plaintiffs' Section 20(a) claim because the Complaint purportedly does not adequately allege primary Section 10(b) liability. When defendants limit themselves to such arguments in moving to dismiss Section 20(a) claims, upon finding Section 10(b) claims adequately alleged, courts will simply uphold Section 20(a) claims without further analysis. *Avaya*, 564 F.3d at 280. Accordingly, the Complaint adequately alleges a claim for control person liability. *Local 731 I.B. of T. Excavators & Pavers Pension Tr. Fund v.*

Swanson, No. CIV.A. 09-799, 2011 WL 2444675, at *14 (D. Del. June 14, 2011); *Palladin Partners v. Gaon*, No. 05 CV 3305 WJM, 2006 WL 2460650, at *16 (D.N.J. Aug. 22, 2006).

IV. CONCLUSION

For the foregoing reasons, the Court should deny the Motion to Dismiss in its entirety.

Dated: June 24, 2020

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on this 24th day of June, 2020 a true and correct copy of the foregoing PLAINTIFFS' CORRECTED MEMORANDUM OF LAW IN OPPOSITION TO DEFENDANTS' MOTION TO DISMISS was served by CM/ECF to the parties registered to the Court's CM/ECF system.

/s/ Jacob Goldberg
Jacob Goldberg